CHAPTER 36
LATE EFFECTS OF RADIATION

Late Effects of Radiation
- The result of low doses delivered over a long period
- It is also known as *stochastic effects*
- *Principal Late Effects:* radiation-induced malignancy & genetic effects
- *Others:* shortening of life span & local tissue effect

Stochastic Radiation Response
- Probability of frequency of the biologic response to radiation as a function of radiation dose
- No threshold dose

Radiation Exposure Experience By Personnel
- Low dose & low LET
- Chronic in nature
    - Delivered intermittently over long periods

Our radiation protection guides are based on the late effects of radiation & on linear, nonthreshold dose-response relationships!

Epidemiologic Studies
- It is requires when the number of persons affected is small
- It is difficult
    - *Rationale:*
        - The dose usually is not known but presumed to be low
        - The frequency of response is very low
- *Result:* do not convey the statistical accuracy associated with observations of early radiation effects

LOCAL TISSUE EFFECTS

Radiodermatitis
- Developed on early radiologists who performed fluoroscopic examination
- *Skin Appearance:* callused, discolored & weathered (hands & forearms)
- *Skin Characteristics:* very tight, brittle & severely crack or flake

Irradiation of Blood-Forming Organs
- *Early Response:* hematologic depression
- *Late Response:* leukemia

Irradiation of Circulating Lymphocytes
- *Early & Late Response:* chromosome damage

Radiation-Induced Cataract
- It occurs on the posterior pole of the lens
- *Dose-Response Relationship:* nonlinear, threshold
- *Radiosensitivity of Lens:* age-dependent
- *Increased Age:*
    - Greater radiation effect
    - Shorter latent period
        - 5-30 years
        - *Average:* 15 years
- High-LET Radiation
    - *Examples:* neutron & proton radiation
    - It has a high RBE for the production of cataracts

E.O. Lawrence (1932)
- He developed the first cyclotron

Cyclotron
- A 5-inch-diamter device capable of accelerating charged particles to very high energies

Modern Cyclotron
- It is used principally to produce radionuclides for use in nuclear medicine
- *Fluorine 18:* for PET Scan

Largest Particle Accelerator
- *Purposes:*
    - To discover the ultimate fine structure of matter

  - To describe exactly what happened at the moment of creation of the universe
- *Locations:*
  - Argonne National Laboratory in US
  - CERN in Switzerland

Cyclotron Physicists
- They used radiographic IS to aid them in locating the high-energy beam

1949
- The first paper reporting cataracts in cyclotron physicists appeared

1960
- Several hundred such cases of cataracts had been reported

Lens of the Eye
- Threshold Dose
  - *Cataracts:* > 1000 rad
  - *Acute X-ray Exposure:* 200 rad
  - *Fractionated Exposure:* > 1000 rad
  - *Occupational Exposure:* impossible to reach
- *Dose in CT Scan:* 5 rad per slice
  - Protective lens shields are not normally required
    - *Rationale:* no more than one or two slices intersect the lens

LIFE SPAN SHORTENING

At worst, humans can expect a reduced life span of approximately 10 days for every rad!

Radiation Workers
- *Expected Days of Life Lost:* 12 days

Radiation technology is a safe occupation!

Radiation-Induced Life Span
- It occurs simply as accelerated premature aging & death

RSNA
- Radiological Society of North America

AAOO
- American Academy of Opthalmology & Orolaryngology

ACP
- American College of Physicians

Risk Estimates
- These are used to estimate radiation response in a population
- *Three Types:* relative, excess & absolute

Relative Risk
- Estimation of late radiation effects in large population without precise knowledge of their radiation dose
- Persons in the exposed population with late effects versus the number in an unexposed population in the same condition
- *Formula:*

$$\text{Relative Risk} = \frac{\text{Observed cases}}{\text{Expected cases}}$$

- *RR of 1.0:* no risk
- *RR of 1.5:* 50% higher in the irradiated population
- *RR of 1-2:* for radiation-induced late effects
- *RR < 1:* exposed population receives some protective benefit

The theory of radiation hormesis suggests that very low (<10 rad) radiation doses are beneficial!

Excess Risk
- It determines the magnitude of the late effect
- Difference between observed & expected numbers of cases
- *Formula:* Excess Risk = Observe Cases – Expected Cases
- *Excess Cases:* assumed to be radiation induced

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Absolute Risk
- Incidence of malignant disease in a population within 1 year for a given dose
- *Units:* cases/population/dose
- *Expressed As:* number of cases/10^6 persons/rem
- *AR of Fatal Radiation-Induced Malignant Disease:* 5×10^{-4} rem^{-1} or 5×10^{-2} Sv^{-1}
- *Value of AR:* equals to the slope of the dose-response relationship

RADIATION-INDUCED MALIGNANCY

Stochastic Effect
- It has no dose threshold
- All radiation-induced malignancies

Radiation-Induced Leukemia
- *Dose-Response Relationship:* linear, nonthreshold
- *Latent Period:* 4-7 years
- *At-Risk Period:* 20 years

At-Risk Period
- The time after irradiation during which one might expect that radiation effect to occur
- *Radiation-Induced Cancer:* lifetime

ABCC
- Atomic Bomb Casualty Commission

RERF
- Radiation Effects Research Foundation

Chronic lymphocytic leukemia is rare & therefore is not considered to be a form of radiation-induced leukemia!

Ankylosing Spondylitis
- An arthritis-like condition of the vertebral column
- *For Relief:* high-dose of radiation to the spinal column
- *Permanent Cure:* radiation therapy

National Background Radiation
- Levels increase in general with altitude & latitude

Radiation-Induced Cancer
- Thyroid Cancer, Bone Cancer, Skin Cancer, Breast Cancer, Lung Cancer & Liver Cancer

Thyroid Cancer
- Develop in patients whose thyroid glands were irradiated in childhood

Bone Cancer
- Watch dial painter
  - Ingestion of radium
- *Radium:*
  - It behaves similar to calcium & deposit in bone
  - *Half Life:* 1620 years
- *Relative Risk:* 122:1
- *Absolute Risk:* 1×10^{-4} rem^{-1}

Tritium (^3H) & Promethium (^{147}Pm)
- Currently used in watch dial painting

Skin Cancer
- *Begins:* development of radiodermatitis
- Patient treated with orthovoltage (200-300 kVp) or superficial x-ray (50-150 kVp)
- *Dose-Response Relationship:* threshold
- *Latent Period:* 5-10 years

Breast Cancer
- *Risks:*
  - Patient treated with non-image-intensified fluoroscopy for TB
  - Patient treated with x-rays for acute postpartum mastitis
- *Absolute Risk:* 6 cases/10^6 persons/rad/year

Lung Cancer
- *Caused:* dusty mine environment
- Risks:
  - Workers in the Bohemian pitchblende mines
  - Uranium Miners

    - *Half Life:* 10^9 years
    - *Relative Risk:* 8:1
- Smoking Uranium Miners
    - *Relative Risk:* 20:1

Radon
- A gas that emanates through the rock to produce a high concentration in air
- Decay product of uranium

Liver Cancer
- Thorotrast is carcinogenic at the site of the injection
- ThO2 particles are deposited in phagocytic cells of the reticuloendotheial system
    - Concentrated in the liver & spleen

Thorotrast
- It was widely used in diagnostic radiology before as a contrast agent for angiography
- Thorium dioxide (ThO_2) in a colloidal suspension
- *ThO_2:* emits alpha, beta & gamma (100:10:1)

Total Risk of Malignancy
- Overall Absolute Risk: 8 cases/10,000/rad
- *At-Risk Period:* 20-25 years after exposure
- *Risk of Death:* 5/10,000/rad

Three Mile Island
- *Year:* 1979
- *Location:* Susquehanna River, Pennsylvania

BEIR Committee
- Biologic Effects of Ionizing Radiation
- It has reviewed the date on late effects of low-dose, low-LET radiation
- *Excess Malignant Disease Mortality:* 10 rad
- *Response to a Dose:* 1 rad/yr
- *Excess Radiation-Induced Cancer Mortality:* continuous dose of 100 mrad/yr
- It also has analyzed whether the response was absolute or relative

The BEIR Committee has further stated that because of the uncertainty in its analysis, less than 1 rad/yr may not be harmful!

Absolute Risk Model
- It predicts that the excess-radiation-induced cancer risk is constant for life

Relative Risk Model
- It predicts that the excess radiation-induced cancer risk is proportional to the natural incidence

Radiation Risk Estimate
- It assumes whole-body exposure

RADIATION & PREGNANCY

Before Pregnancy
- *Concern:* interrupted fertility

During Pregnancy
- *Concern:* possible congenital effects in newborn

Postpregnancy
- *Concern:* suspected genetic effects

Effects on Fertility
- It does occur & dose related

Low-dose, chronic irradiation does not impair fertility!

Irradiation in Utero
- It is time related & dose related
- *Concerns Two Types of Exposures:*
    - That of the radiation worker
    - That of the patient
- *Effects:*
    - Prenatal death
    - Neonatal death
    - Congenital malformation
    - Malignancy induction
    - General impairment of growth
    - Genetic effects
    - Mental retardation

- *Response:* all-or-none variety
    - Radiation-induced abortion occurs or pregnancy is carried to term without no ill effect

All observations point to the first semester during pregnancy as the most radiosensitive period!

The first 2 weeks of pregnancy may be of least concern because the response is all-or-nothing!

Major Organogenesis

- From 2nd-10th week
- *Two Effects May Occur:*
    - Skeletal & organ abnormalities
    - Congenital abnormalities
        - *Severe:* neonatal death

The relative risk of childhood leukemia after irradiation in utero is 1.5!

RELATIVE RISK OF CHILDHOOD LEUKEMIA AFTER IRRADIATION IN UTERO BY TRIMESTER

Time of X-ray Examination	Relative Risk
First trimester	8.3
Second trimester	1.5
Third trimester	1.4
Total	1.5

Effects After 10 Rad in Utero

- Spontaneous Abortion
    - Least concern
        - *Rationale:* all-or-none effect
    - *Time of Exposure:* 0-2 weeks
    - *Natural Occurrence:* 25%
    - *Radiation Response:* 0.1%
- Congenital abnormalities
    - *Time of Exposure:* 2-10 weeks
    - *Natural Occurrence:* 5%
    - *Radiation Response:* 1%
- Mental Retardation
    - *Time of Exposure:* 2-15 weeks
    - *Natural Occurrence:* 6%
    - *Radiation Response:* 0.5%
- Malignant Disease
    - *Time of Exposure:* 0-9 months
    - *Natural Occurrence:* 8/10,000
    - *Radiation Response:* 12/10,000
- Impaired growth & development
    - *Time of Exposure:* 0-9 months
    - *Natural Occurrence:* 1%
    - *Radiation Response:* nil
- Genetic mutation
    - *Time of Exposure:* 0-9 months
    - *Natural Occurrence:* 10%
    - *Radiation Response:* nil

Radiation Genetics

- Our weakest area of knowledge in radiation biology

We do not have any data that suggest that radiation-induced genetic effects occur in humans!

H.J. Muller

- He reported the results of his irradiation of *Drosophila*, the fruit fly
- Conclusions
    - *Genetic Effects:* linear-nonthreshold
    - Radiation does not alter the quality of mutations but rather increases the frequency of those mutations

Russell

- He began to irradiation a large mouse colony with different radiation dose rates
- *Conclusions:*
    - A dose rate effect does exist
    - The mouse has capacity to repair genetic damage
    - He confirmed the linear, nonthreshold form of dose-response relationship
    - He has not detected any types of mutations that did not occur naturally

The doubling dose is that dose of radiation that produces twice the frequency of genetic mutations as would have been observed without the radiation!

ADDITIONAL CONCLUSION REGARDING RADIATION GENETICS
Radiation-induced mutation are usually harmful.
Any dose of radiation, however small, to a germ cell results in some genetic risk.
The frequency of radiation-induced mutations is directly proportional to dose, so that a linear extrapolation of data obtained at high doses provides a valid estimate of low-dose effects.
The effect depends on radiation protraction & fractionation.
For most pre-reproductive life, the woman is less sensitive than the man to the genetic effects of radiation.
Most radiation-induced mutations are recessive. These require that the mutant genes must be present in both the male & the female to produce the trait. Consequently, such mutations may not be expressed for many generations.
The frequency of radiation-induced genetic mutations is extremely low. It is approximately 10^{-7} mutations/rad/gene.